UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/569,863	06/13/2006	Per Holm	20481/1206898-US1	9762

7278 7590 10/08/2009

DARBY & DARBY P.C.
P.O. BOX 770
Church Street Station
New York, NY 10008-0770

EXAMINER	
POLANSKY, GREGG	
ART UNIT	PAPER NUMBER
1614	

MAIL DATE	DELIVERY MODE
10/08/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/569,863	HOLM ET AL.	
	Examiner	Art Unit	
	GREGG POLANSKY	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 February 2009 and 09 June 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-29,31-34,36-44 and 51-56* is/are pending in the application.

4a) Of the above claim(s) *12,38 and 39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-11,13-29,31-34,36,37,40-44 and 51-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicants' submission filed on 8/04/2009 has been entered.

2. By way of the submission filed on 8/04/2009, Applicants have canceled Claim 2, amended Claims 1, 7-10, 22, 23, 27, 28, 37, 41, 42, 44, 51, and 56, and presented arguments in response to the Final Rejection mailed 2/04/2009 and the Advisory Action mailed 6/09/2009.

3. Claims 1, 3-11, 13-29, 31-34, 36, 37, 40-44 and 51-56 are presently under consideration.

4. Applicants' arguments have been fully considered and are persuasive in part. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

5. Applicants' arguments with regard to the rejection of claims under 35 USC 103(a) over Patel et al. has been fully considered. Applicants assert "the presently claimed tacrolimus composition provides significantly superior bioavailability compared to a

marketed form of tacrolimus known as Prograf®." Applicants point to Example 6 at pages 35 and 36 in support of this assertion. Example 6 discloses a tacrolimus formulation comprising tacrolimus, lactose monohydrate, PEG 6000, poloxamer 188, magnesium stearate, talc, and croscarmellose sodium. However, the scope of the instant claims is much broader than the formulation of Example 6. **Amending the claims to limit the scope of the instant claims to a tacrolimus formulation comprising the ingredients disclosed by Example 6 would appear to overcome the 35 USC 103(a) rejection presented below.**

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1, 3-11, 13-29, 31-34, 36, 37, 40-44 and 51-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Patel et al. (U.S. Patent Application Pub. No. 2003/0180352 A1), in view of Holm et al. (WO 03/004001 A1, cited by Applicants) and "Tacrolimus (Systemic)" (Drugs.com, August 1997, downloaded from "www.drugs.com/mmx/tacrolimus.html" on 10/05/2009, pages 1-43 of 43; hereinafter referred to as "Drugs.com").

Patel et al. teach a solid dosage formulation comprising tacrolimus, PEG-24 cholesterol ether (SOLULAN C-24), distilled monoglycerides, and deoxycholic acid,

coated on nonpareil seed having a diameter of about 400 to 500 µm. See page 41, paragraph 425. The concentration of tacrolimus in the formulation is 2 % (w/w). Distilled monoglycerides are an oily hydrophobic material with a melting point >60°C. The reference teaches the formulation may also "include additional additive, excipients, and other components for the purpose of facilitating the processes involving the preparation of the composition or the pharmaceutical dosage form, as described [in the reference and] as is well-known to those skilled in the art". See page 41, paragraph 417. Patel et al. further disclose a wide variety of active ingredients (including tacrolimus) which may be dispersed in a solid carrier which comprises *inter alia* hydrophilic surfactants, including polyethylene glycol 6000 (PEG 6000). See Abstract; page 6, paragraph 76; page 9, paragraph 108 and page 43, paragraph 436. Patel et al. teach the compositions can be used for improved delivery of active ingredients. Figures 1-3 of the disclosure demonstrate improved release rates of various agents (as compared to commercial products or pure bulk drug) formulated by the methods taught by Patel et al. The reference discloses the "active agent can be solubilized, dispersed, or partially solubilized and dispersed" in an encapsulation coat. See page 4, paragraph 55. Patel et al. teach poloxamers, including poloxamer 188 among the most preferred surfactants for the disclosed formulations. See page 21, paragraph 183; page 23, paragraph 201. The hydrophilic surfactants utilized can be a single surfactant of a mixture of surfactants. See page 13, paragraph 144. Patel et al. teach the formulations may include additives, including binders, fillers, flavorants, preservatives, antioxidants, bufferants, and disintegrants. See pages 27-28, paragraphs 236-260. Specific

additives include, magnesium aluminum silicate, fumed silica (silicon dioxide), ethyl cellulose, cellulose acetate, cellulose nitrate, GELUCIRE 62/05, GELUCIRE 44/14, GELUCIRE 50/13, cellulose acetate phthalate (a water-miscible polymer with pH-dependent water solubility, utilized in enteric coatings). See pages 25-26, paragraph 216; page 27, paragraphs 237 and 242; page 28, paragraphs 259-260; and page 30, paragraph 280. The reference to Patel et al. further teaches a pharmaceutical composition in the form of a solid carrier wherein the solid carrier is prepared by a process without the need of introducing organic solvents. See page 2, paragraph 24 and page 45, claim 27. The reference teaches the compositions can be processed by, *inter alia*, agglomeration. See page 29, paragraph 272.

Holm et al. teach "[a] process for the preparation of a particulate material by a controlled agglomeration method, i.e. a method that enables a controlled growth in particle size. The method is especially suitable for use in the preparation of pharmaceutical compositions containing a therapeutically and/or prophylactically active substance which has a relatively low aqueous solubility..." See Abstract. Holm et al. teach "very promising results with respect to bioavailability when [the disclosed formulation process] is employed for the preparation of particulate material containing an active substance with a very low aqueous solubility." See lines 1-8, at page 12. "The particulate material obtained by a process [disclosed by Holm et al.] is especially suitable for further processing into tablets." Formulating the tablets to have particular release characteristics is also disclosed. See lines 4-13, at page 27. The reference teaches the particulate material (supra) having a geometric weight mean diameter of

from 20 µm to 2000 µm. See lines 6-17, at page 28. Magnesium aluminosilicate and/or magnesium aluminometasilicate may be used as a lubricant. See lines 25-26, at page 28. Holm et al. exemplify particulate preparations, tablets of the preparations, and the resulting improvements in drug bioavailability. See Examples 1-6, at pages 31-56. For example, see Example 4 which discloses tablets of a particulate formulation (Treatment B) comprising a drug, polyethylene glycol 6000, poloxamer 188, and Avicel® PH 101 (microcrystalline cellulose). Additional excipients useful in the preparations and other formulation characteristics which encompass the instant claims are disclosed by Holm et al. in Claims 1-56. With respect to claimed concentration ranges of the surfactants (i.e., polyethylene glycols and poloxamers) in the instant methods, it is not inventive to discover the optimum or workable ranges by routine experimentation when general conditions of a claim are disclosed in the prior art. See *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233,235 (CCPA 1955) and MPEP 2144.05(11).

Drugs.com is provided to further demonstrate prior art knowledge of tacrolimus being practically insoluble in water, and that tacrolimus has “[r]apid, variable, and incomplete [absorption] from the gastrointestinal tract" and a mean oral bioavailability of 27%, with a range of 5-65%. See Solubility, at page 2 and Absorption at page 3.

The Patel et al., in view of Holm et al. teaches or suggests all of the limitations of the instant claims. It would have been obvious to one of ordinary skill at the time of the invention, who was motivated to improve the release profile of formulations of tacrolimus, to utilize the methods taught by Patel et al. and Holm et al. Drugs.com

teaches the low aqueous solubility and oral bioavailability of tacrolimus, providing further motivation to combine the teachings of Patel et al. and Holm et al.

It is noted that *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter, which there is reason to believe inherently includes functions that are newly cited, or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter to be shown in the prior art does not possess the characteristic relied on" (205 USPQ 594, second column, first full paragraph). There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003); see also *Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004) ("[T]he fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention"). Also see *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1343-44, 74 USPQ2d 1398, 1406-07 (Fed. Cir. 2005) (holding that a prior art patent to an anhydrous form of a compound "inherently" anticipated the claimed hemihydrate form of the compound because practicing the process in the prior art to manufacture the anhydrous compound "inherently results in at least trace amounts of" the claimed hemihydrate even if the prior art did not discuss or recognize the hemihydrate).

In the instant case, absent evidence to the contrary, it would be expected that the release rates of tacrolimus from the formulation taught by Holm et al., comprising tacrolimus taught by Patel et al., would be the same as those recited by instant Claims 8-10 and 42-44. Additionally, one would expect, absent evidence to the contrary, that the tacrolimus formulation would have a similar bioequivalence to the formulation of the instant methods.

A reference is good not only for what it teaches by direct anticipation but also for what one of ordinary skill in the art might reasonably infer from the teachings. (*In re Opprecht* 12 USPQ 2d 1235, 1236 (Fed Cir. 1989); *In re Bode* 193 USPQ 12 (CCPA) 1976). In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a). From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole is *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Double Patenting

8. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140

F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

9. Claims 1, 3-11, 13-29, 31-34, 36, 37, 40-44 and 51-56 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over Claims 1, 8, 10, 17-23, 26-32, 34, 36, 37, 63 and 64 of copending Application No. 10/513807. Although the conflicting claims are not identical, they are not patentably distinct from each other because they recite similar formulation, utilizing similar constituents, differing only by the active agent of the formulations.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicants have requested the rejection be held in abeyance until a claim is found allowable. Accordingly, the rejection is maintained.

10. Claims 1, 3-11, 13-29, 31-34, 36, 37, 40-44 and 51-56 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over Claims 1-50 of copending Application No. 11/885992. Although the conflicting claims are not identical, they are not patentably distinct from each other because they

are both drawn to similar pharmaceutical compositions of tacrolimus or tacrolimus analogues and methods of preparation of said compositions.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicants have requested the rejection be held in abeyance until a claim is found allowable. Accordingly, the rejection is maintained.

11. Claims 1, 3-11, 13-29, 31-34, 36, 37, 40-44 and 51-56 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over Claims 1-10 and 15-31 of copending Application No. 11/569862. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are both drawn to similar pharmaceutical compositions of tacrolimus or tacrolimus analogues and methods of preparation of said compositions. The open language of the instant claims allows for the inclusion of additional constituents.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

12. Claims 1, 3-11, 13-29, 31-34, 36, 37, 40-44 and 51-56 are rejected.

13. No claims are allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to GREGG POLANSKY whose telephone number is

(571)272-9070. The examiner can normally be reached on Mon-Thur 9:30 A.M. - 7:00 P.M. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571) 272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Gregg Polansky/
Examiner, Art Unit 1614

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614